DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date FEB 13 1997

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Angelini Pharmaceuticals Inc.'s 2-In-1 Drop - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

for Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Muriel Gelles, CDRH, HFZ-460, 1/29/97, 594-1744

A

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

ANGELINI PHARMACEUTICALS, INC.; PREMARKET APPROVAL OF THE 2-IN-1 DROP

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Angelini Pharmaceuticals, Inc., River Edge, NJ, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of the 2-In-1 Drop. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on February 13, 1997, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

3

FOR FURTHER INFORMATION CONTACT:

James F. Saviola, O.D., F.A.A.O.,

Center for Devices and Radiological Health (HFZ-460),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-594-1744.

SUPPLEMENTARY INFORMATION: On May 25, 1994, Angelini Pharmaceuticals, Inc., River Edge, NJ 07661, submitted to CDRH an application for premarket approval of the 2-In-1 Drop. The device is a contact lens drop, packaged in a single-use container, that is indicated for use with soft (hydrophilic) contact lenses (including disposables) and rigid gas permeable contact lenses as a lubricating and rewetting agent during the wearing period and as a wetting agent to cushion lenses prior to placement on the eye. The 2-In-1 Drop may also be used in place of a daily cleaner as part of an appropriate chemical disinfection regimen.

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel of the Medical Device Advisory Committee, an FDA

4

advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On February 13, 1997, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of the act, (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under

§10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

6

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 13 1997

John M. Szabocsik, Ph.D.
Consultant for Angelini Pharmaceuticals, Inc.
Szabocsik and Associates
203 North Wabash Avenue
Suite 1200
Chicago, IL 60601

Re: P940014
2-In-1 Drop
Filed: May 25, 1994
Amended: June 6 and August 1, 1994; May 19, 1995;
May 2 and 6, July 22, September 18 and 25, and November 15, 1996; and
February 3, 1997

Dear Dr. Szabocsik:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of the premarket approval application (PMA), that you submitted on behalf of Angelini Pharmaceuticals, Inc., for the 2-In-1 Drop. The 2-In-1 Drop, packaged in the single-use container, is indicated for use with soft (hydrophilic) contact lenses (including disposables) and rigid gas permeable contact lenses as a lubricating and rewetting agent during the wearing period and as a wetting agent to cushion lenses prior to placement on the eye. The 2-In-1 Drop may also be used in place of a daily cleaner as part of an appropriate chemical disinfection regimen. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). Your client may begin commercial distribution of the device upon receipt of this letter.

The PMA approval for the 2-In-1 Drop is limited to the device as packaged in 0.01 fl. oz. (0.3 ml) disposable single-use plastic containers. CDRH reminds you that any future PMA supplement requesting approval for packaging the 2-In-1 Drop in a multi-dose container will be required to address potential safety issues pertaining to use of a device as a cleaning solution in addition to in-eye use. In addition, CDRH reminds you that approval of this PMA does not constitute approval of an in-eye cleaning claim.

Expiration dating for this device has been established and approved at 3 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

9

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

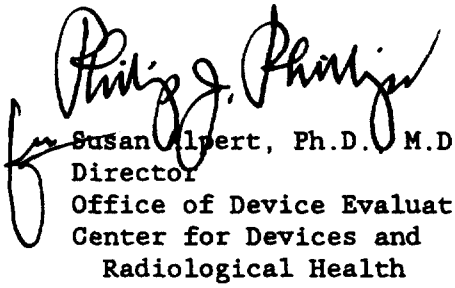
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Muriel Gelles or James F. Saviola, O.D., at (301) 594-1744.

Sincerely yours,



for Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

10

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant**(s)** involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

12

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

13

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

14

Summary of Safety and Effectiveness Data

I. General Information

A. Premarket Approval Application (PMA) Number: P940014
Date Filed: May 25, 1994
Date Approved: FEB 13 1997

B. Investigational Device Exemptions (IDE) Application: G880112

C. Device Generic Name: wetting, rewetting and/or lubricating solution; and substitute for daily cleaner

D. Device Trade Name: 2-In-1 Drop

E. Applicant's Name and Address: Angelini Pharmaceuticals, Inc.
70 Grand Avenue
River Edge, NJ 07661

F. Good Manufacturing Practice (GMP) Inspection:
Date of Inspection: October 12, 1995
Conclusion: The manufacturing site was found to be in compliance with device GMP requirements.

II. Indications

The 2-In-1 Drop, packaged in the single-use container, is indicated for use with soft (hydrophilic) contact lenses (including disposables) and rigid gas permeable contact lenses as a lubricating and rewetting agent during the wearing period and as a wetting agent to cushion lenses prior to placement on the eye. The 2-In-1 Drop may also be used in place of a daily cleaner as part of an appropriate chemical disinfection regimen.

III. Summary

The applicant performed non-clinical and clinical testing on the device in accordance with the FDA Testing Guidelines for Class III Soft (hydrophilic) Contact Lens Solutions dated July 1985. Additional pharmacology and reproductive toxicology testing were conducted under the IDE. The non-clinical testing supports the safety and effectiveness of the device from microbiology, toxicology, chemistry and manufacturing perspectives.

Clinical data were evaluated from a total of 11 studies (see table below) involving 2,613 test and control eyes. Subjects in the test groups used no enzymes. These studies included two controlled 12-month core studies using the 2-In-1 Drop (test device) and a marketed hydrogen peroxide disinfection system (system 1). One of these studies included representative groups of soft (hydrophilic) contact lenses and the other included representative groups of rigid gas permeable (RGP) contact lenses. Two smaller 12-month controlled studies were also conducted. One included a marketed chemical disinfection system (system 2) and the test device with RGP lenses, and the other included the test device with disposable soft (hydrophilic) contact lenses, without a disinfection system.

16

In addition, four 6-month controlled studies were conducted. Two studies used marketed chemical disinfection systems (systems 3 and 4) and the test device with soft (hydrophilic) contact lenses. The other two studies used an investigational chemical disinfection system; one study included soft (hydrophilic) contact lenses and the other RGP lenses. Three brief adjunctive studies were conducted to address specific issues [e.g., 2-month double-blind, crossover randomized study comparing the test device to a placebo lubricating drop (test device without bendazac), 1-month pilot in-vivo randomized cleaning study comparing the test device with three different marketed rewetting drops, and a 6-week study with disposable lenses and five different lubricating drops].

The studies included 907 females and 384 males in the test and control groups. Five subjects wore a lens in only one eye. Two subjects (1 test, 1 control) were found to be ineligible at the initial examination, after signing the informed consent; they are included in the above totals although no products were dispensed. Additionally, 18 subjects (36 eyes) were enrolled in the 4-week disposable lens study in which gender was not identified. The gender ratio is representative of the contact lens wearing population in the United States. Although the potential exists for minor differences in physiological response by gender for the target population, the minimal number of clinically significant findings does not indicate gender difference to be of clinical importance for this device.

Clinical Studies

Lens	Disinfecting Systems/Duration	Eyes Enrolled Test:Cont.		Completed Test:Cont.		Discontinued Test:Cont.	
Soft	System 1/(12 mos)	537[1]	94	447	88	90[1]	6
RGP	System 1/(12 mos)	530	80	426	68	104	12
RGP	System 2/(12 mos)	88	20	72	16	16	4
Soft/Disp.	N/A/(12 mos[6])	40	6	30	4	10	2
Soft	System 3/(6 mos)	246	200[2]	218	172	28	28[2]
Soft	System 4/(6 mos)	240	193[3]	204	176	36	17[3]
Soft/Placebo*	(4 mos)	179[4]		152		27[5]	
Soft/Disp.*	N/A/(6 wks[6])	48		46		2	
Soft/Disp.*	N/A/(4 wks[6])	36		34		2	
RGP	Inves. System/(6 mos)	16	20	16	20	0	0
Soft	Inves. System/(6 mos)	17	23	17	23	0	0
Total		1,977	636	1,662	567	315	69

[1] 2 test eyes determined by applicant as ineligible after signing informed consent (recorded as discontinued). 3 subjects wore lenses in only 1 eye.
[2] 2 control eyes determined by applicant as ineligible after signing informed consent (recorded as discontinued).
[3] 1 control subject wore lens in only 1 eye.
[4] Double-blinded cross-over study; 1 subject wore lens in only 1 eye.
[5] Includes 12 eyes from first half; 13 from placebo; and 2 from both. 1 subject wore lens in only 1 eye.
[6] Disinfection not applicable (N/A) for disposable lenses.
* Adjunctive study

IV. Safety and Effectiveness

A. Non-clinical Data

The applicant conducted a battery of in-vivo and in-vitro acute toxicology studies that support the safety and biocompatibility of the solution with soft (hydrophilic) and RGP contact lenses. Additionally, chemistry and manufacturing information were submitted demonstrating that the solution is suitable for use to clean, wet, rewet and/or lubricate soft (hydrophilic) and RGP contact lenses. The adequacy of the manufacturing process, including sterilization and shelf-life expiration dating, was established through a review of the manufacturing and microbiology data submitted in the PMA as well as through an on-site GMP inspection.

B. Clinical Data

Clinical data from six studies [Soft/System 1, RGP/System 1, RGP/System 2, Soft/Disposables (no disinfection system), Soft/System 3, and Soft/System 4] provide data supporting labeling claims and are analyzed below. Clinical data from the three adjunctive studies and two 6-month studies that used an investigational disinfecting system are not included in the clinical analysis. The three adjunctive studies were designed to collect data for additional labeling claims which were not supported from an effectiveness standpoint. Data from the clinical studies using the investigational disinfecting system are not included in the analysis because of the investigational status of the disinfecting system. Clinical analysis of safety and effectiveness data for the labeled indications includes the following eyes:

1. Accountability:

a. Test Groups: (1,681 eyes enrolled; 1,397 completed and 284 discontinued* (8 associated with pathology**).

b. Control Groups: (593 eyes enrolled*): 524 completed and 69 discontinued* (none associated with pathology)

*2 test and 2 control eyes were considered by applicant to be ineligible and received no solution.

**1 marginal corneal ulcer determined by investigator as due to overnight wear of daily wear lens and 1 mild iritis (Soft/System 3 study), 6 giant papillary conjunctivitis (2 RGP/System 1, 2 RGP/System 2, and 2 Soft/System 4 studies). All resolved without sequelae.

18

2. Visual Acuity*:

a. Test Groups:

Visual Acuity	Initial Visit with Lens	Final Visit with Lens
20/30 or Better 20/40 or Worse		
Soft/System 1	(424/447)=94.9% (11/447)=2.5%	(432/447)=96.6% (13/447)=2.9%
RGP/System 1	(413/426)=97% (2/426)=.05%	(419/426)=98.4% (3/426)=.07%
RGP/System 2	(72/72)=100% (0/72)=0%	(72/72)=100% (0/72)=0%
Soft/Disp.	(29/30)=96.7% (1/30)=.33%	(29/30)=96.7% (1/30)=.33%
Soft/System 3	(210/218)=96.3% (2/218)=0.9%	(209/218)=95.9% (6/218)= 2.8%
Soft/System 4	(201/204)=98.5% (3/204)=1.5%	(199/204)=97.5% (2/204)=.98%

b. Control Groups:

Visual Acuity	Initial Visit with Lens	Final Visit with Lens
20/30 or Better 20/40 or Worse		
Soft/System 1	(85/86)=98.8% (1/86)=1.2%	(85/86)=98.8% (1/86)=1.2%
RGP/System 1	(66/68)=97% (2/68)=2.9%	(66/68)=97% (2/68)=2.9%
RGP/System 2	(16/16)=100% (0/16)=0%	(16/16)=100% (0/16)=0%
Soft/Disp.	(4/4)=100% (0/4)=0%	(4/4)=100% (0/4)=0%
Soft/System 3	(169/172)=98.3% (1/172)=0.6%	(168/172)=97.7% (3/172)=1.7%
Soft/System 4	(173/176)=98.3% (3/176)=1.7%	(173/176)=98.3% (1/176)=0.6%

*Initial and final visual acuities were not reported for remaining eyes.

19

3. Wear Time (Daily)*:

a. Test Groups:

Studies	Initial Adapted (1 week)	Final
Soft/System 1	13.5 hours	13.6 hours
RGP/System 1	13.4 hours	14.1 hours
RGP/System 2	14.4 hours	14.6 hours
Soft/Disp.	7.9 days	7.5 days
Soft/System 3	14.2 hours	13.9 hours
Soft/System 4	13.2 hours	13.2 hours

b. Control Groups:

Studies	Initial Adapted (1 week)	Final
Soft/System 1	12.9 hours	13.3 hours
RGP/System 1	13.9 hours	13.8 hours
RGP/System 2	14.9 hours	15.3 hours
Soft/Disp.	4.0 days	4.5 days
Soft/System 3	14.3 hours	14.5 hours
Soft/System 4	13.2 hours	13.2 hours

*Reported in days for the soft/disposable lens study.

4. Keratometry (greater than 1.00 diopter change):

a. Test Groups:

4 in Soft/System 1, 8 in RGP/System 1, and 3 in Soft/System 4 studies (15 reports/1,397 eyes)=1.07%

b. Control Groups:

2 in Soft/System 1, 1 in RGP/System 1 and 1 in Soft/System 3 studies (4 reports/591 eyes)=.67%

5. Lens Cleanliness at Final Visit (Rudko Measuring Scale)*:

a. Test Groups:

Studies	Type I	Type II	Type IV
Soft/System 1	(272/438)=62.1%	(129/438)=29.5%	(37/438)=8.4%
RGP/System 1	(198/421)=47%	(206/421)=48.9%	(17/421)=4%
RGP/System 2	(49/69)=71%	(19/69)=27.5%	(1/69)=1.4%
Soft/Disp.	(28/30)=93.3%	(2/30)=6.7%	(0/30)=0%
Soft/System 3	(101/214)=47.2%	(102/214)=47.7%	(11/214)=5.1%
Soft/System 4	(146/202)=72.3%	(49/202)=24.3%	(7/202)=3.5%

20

b. Control Groups:

Studies	Type I	Type II	Type IV
Soft/System 1	(54/87)=62.1%	(27/87)=31.0%	(6/87)=6.9%
RGP/System 1	(34/66)=51.5%	(31/66)=47%	(1/66)=1.5%
RGP/System 2	(6/10)=60%	(4/10)=40%	(0/10)=0%
Soft/Disp.	(3/4)=75%	(1/4)=25%	(0/4)=0%
Soft/System 3	(86/170)=50.6%	(74/170)=43.5%	(10/170)=5.9%
Soft/System 4	(119/174)=68.4%	(38/174)=21.8%	(17/174)=9.8%

Key:
Type I = No deposits
Type II = Appears clean with naked eye, but minor deposits/ discolorations can be seen with special lighting and/or magnification
Type III = Not used
Type IV = Lenses covered by deposits seen with visual aids

*Not reported for remaining eyes.

During the clinical studies, the majority of subjects used the 2-In-1 Drop 2-3 times a day in combination with use of the device in place of the daily cleaner. Some patients may require the use of an alternate daily cleaner if their lenses become visibly deposited or uncomfortable. The labeling for the 2-In-1 Drop provides the alternative of using a conventional daily cleaner, if needed.

5. Adverse Reactions:

a. Test Groups:

Two adverse reactions were reported for discontinued subjects. There was 1 interim report of marginal ulcer and 1 interim report of mild iritis in the Soft/System 3 study. Both resolved without sequelae. The applicant judged these to not be adverse reactions because they were anticipated risks cited in the study protocol.

b. Control Groups:

None reported.

6. Slit Lamp Findings (Eyes)*: #Positive Findings/# Completed Eyes

a. Test Groups:

Studies	Initial Visit	Final Visit
Soft/System 1	(88/447)=19.7%	(42/447)=9.4%
RGP/System 1	(94/426)=22.1%	(138/426)=32.4%
RGP/System 2	(0/72)=0%	(0/72)=0%
Soft/Disp.	(10/30)=33.3%	(5/30)=16.7%
Soft/System 3	(38/218)=17.4%	(17/218)=7.8%
Soft/System 4	(31/204)=15.2%	(23/204)=11.3%

21

In the combined completed test studies, there was a total of 64 initial and 50 final slit lamp findings ≥ grade 2, all of which resolved without sequelae.

Findings:	Studies:	Initial/Final:	
Edema			
Grade 2	RGP/System 1	1	
	Soft/System 3		2
Grade 3	RGP/System 1		2
Injection			
Grade 2	RGP/System 1		7
	Soft/System 3	2	
Grade 3	RGP/System 1		2
	Soft/System 3	2	
Staining			
Grade 2	Soft/System 1	2	
	RGP/System 1	5	10
	Soft/Disp.	1	
	Soft/System 3	1	2
	Soft/System 4	1	
Grade 3	RGP/System 1		1
	Soft/System 3	1	
Tarsal Abnormalities			
Grade 2	Soft/System 1	15	8
	RGP/System 1	6	6
	Soft/System 3	4	1
	Soft/System 4	6	2
Grade 3	Soft/System 1	5	1
	Soft/System 3	1	
Grade 4	Soft/System 3	2	1
Vascularization			
Grade 2	Soft/System 1	2	2
	Soft/System 3	2	
Grade 3	RGP/System 1	4	
Other*			
Grade 2	Soft/System 1		2
	RGP/System 1		1
Grade 3	Soft/System 1	1	

*Other included 2 reports of grade 2 giant papillary conjunctivitis at the final visit in the Soft/System 1 study; 1 report of grade 2 faint infiltrates in 1 eye with grade 1 tear film abnormality in the other eye at the final visit in the RGP/System 1 study; and 1 report of grade 3 endothelial pigment

spindles in 1 eye and grade 1 in the other eye at the initial visit in the Soft/System 1 study.

b. Control Groups:

Studies	Initial Visit	Final Visit
Soft/System 1	(14/88)=15.9%	(5/88)=5.7%
RGP/System 1	(14/68)=20.6%	(34/68)=50%
RGP/System 2	(0/16)=0%	(0/16)=0%
Soft/Disp.	(0/4)=0%	(1/4)=25%
Soft/System 3	(29/172)=16.9%	(9/172)=5.2%
Soft/System 4	(21/176)=11.9%	(17/176)=9.7%

In the combined completed control studies, there was a total of 19 initial and 14 final slit lamp findings ≥ grade 2, all of which resolved without sequelae.

Findings:	Studies:	Initial	Final
Injection			
Grade 2	RGP/System 1		3
Staining			
Grade 2	RGP/System 1	2	2
	Soft/Disp.		1
	Soft/System 3	3	1
Grade 3	Soft/System 3	1	
Tarsal Abnormalities			
Grade 2	Soft/System 3	4	
	Soft/System 4	2	4
Grade 3	Soft/System 3	1	
Grade 4	Soft/System 3	1	
Vascularization			
Grade 2	RGP/System 1	1	
	Soft/System 4	3	2
Other*			
Grade 2	RGP/System 1	1	1

*Other included 1 report of old scar (grade 2) in the RGP/System 1 study at initial and final visits.

9. Symptoms, Problems, Complaints:

a. Test Groups:

Studies	Reports/Total Exams (all visits, including unscheduled)
Soft/System 1	(739/4,551)=16.2%
RGP/System 1	(2,472/4,290)=57.6%
RGP/System 2	(110/716)=15.4%
Soft/Disp.	(20/298)=6.7%
Soft/System 3	(465/1,154)=40.3%
Soft/System 4	(379/1,052)=36%

Categories reported=17

Studies	Vision Related (e.g., variable vision)	Comfort Related (e.g., dryness, pain, itching)	All Other (e.g., lens needs cleaning, medications)
Soft/System 1	(99/739)=13.4%	(407/739)=55%	(233/739)=31.5%
RGP/System 1	(587/2,472)=23.7%	(1,311/2,472)=53%	(574/2,472)=23.2%
RGP/System 2	(12/110)=10.9%	(67/110)=60.9%	(31/110)=28.2%
Soft/Disp.	(2/20)=10%	(17/20)=85%	(1/20)=5%
Soft/System 3	(113/465)=24.3%	(270/465)=58.1%	(82/465)=17.6%
Soft/System 4	(72/379)=19%	(203/379)=53.6%	(104/379)=27.4%

b. Control Groups:

Studies	Reports/Total Exams (all visits, including unscheduled)
Soft/System 1	(54/884)=6.1%
RGP/System 1	(288/670)=43%
RGP/System 2	(10/160)=6.3%
Soft/Disp.	(0/38)=0%
Soft/System 3	(205/906)=22.6%
Soft/System 4	(277/908)=30.5%

Categories reported=17

Studies	Vision Related (e.g., variable vision)	Comfort Related (e.g., dryness, pain, itching)	All Other (e.g., lens needs cleaning, medications)
Soft/System 1	(7/54)=13%	(38/54)=70.4%	(9/54)=16.7%
RGP/System 1	(86/288)=29.9%	(152/288)=52.8%	(50/288)=17.4%
RGP/System 2	(2/10)=20%	(4/10)=40%	(4/10)=40%
Soft/Disp.	(0/0)=0%	(0/0)=0%	(0/0)=0%
Soft/System 3	(64/205)=31.2%	(116/205)=56.6%	(25/205)=12.2%
Soft/System 4	(97/277)=35%	(140/277)=50.5%	(40/277)=14.4%

8. Lens Replacements (Eyes):*

a. Test Groups:

Studies	Number (Replaced/Dispensed) (Dispensed=Total Eyes)
Soft/System 1	(416/535**)=77.8%
RGP/System 1	(188/530)=35.5%
RGP/System 2	(4/88)=4.5%
Soft/Disp.	Not Reported***
Soft/System 3	(88/246)=35.8%
Soft/System 4	(82/240)=34.2%

Categories reported=25

Studies	Lens Related (e.g., refractive change)	Solution Related (e.g., damaged,) deposits)	All Other (e.g., lost, no reason given)
Soft/System 1	(57/416)=13.7%	(308/416)=74%	(51/416)=12.3%
RGP/System 1	(53/188)=28.2%	(56/188)=29.8%	(79/188)=42%
RGP/System 2	(2/4)=50%	(0/4)=0%	(2/4)=50%
Soft/Disp.	Not reported		
Soft/System 3	(51/88)=58%	(18/88)=20.5%	(19/88)=21.6%
Soft/System 4	(39/82)=47.6%	(19/82)=23.2%	(24/82)=29.3%

b. Control Groups:

Studies	Number (Replaced/Dispensed) (Dispensed=Total Eyes)
Soft/System 1	(59/94)=62.8%
RGP/System 1	(32/80)=40%
RGP/System 2	(4/20)=20%
Soft/Disp.	Not Reported***
Soft/System 3	(84/198**)=42.4%
Soft/System 4	(57/193)=29.5%

Categories reported=25

Studies	Lens Related (e.g., refractive change)	Solution Related (e.g., damaged,) deposits)	All Other (e.g., lost, no reason given)
Soft/System 1	(5/59)=8.5%	(44/59)=74.6%	(10/59)=16.9%
RGP/System 1	(6/32)=18.8%	(10/32)=31.3%	(16/32)=50%
RGP/System 2	(2/4)=50%	(0/4)=0%	(2/4)=50%
Soft/Disp.	Not reported		
Soft/System 3	(43/84)=51.2%	(11/84)=13.1%	(30/84)=35.7%
Soft/System 4	(28/57)=49.1%	(9/57)=15.8%	(20/57)=35.1%

* Not all eyes received new lenses (new lenses dispensed in Soft/System 3 and Soft/System 4 studies, but not in Soft/System 1, RGP/System 1, or RGP/System 2 studies).

**Two (2) eyes in each study (test and control) discontinued before solution was dispensed (considered ineligible by applicant).

***Disposable lenses are to be discarded upon removal; thus the applicant did not collect lens replacement data in the 12-month soft/disposable lens study.

Conclusion: Based on the detailed analysis of the data presented in the PMA, it was determined that the clinical findings for the control and test groups (i.e., adverse reactions; positive slit lamp findings; subject symptoms, problems and complaints; visual acuity; lens replacements; lens cleanliness, discontinued subjects; and lens wearing time) were within expected limits for soft (hydrophilic) and RGP lens wearers. Any differences in test and control groups do not raise concerns about the safety and effectiveness of the device when accompanied by appropriate labeling.

V. Conclusion

The Center for Devices and Radiological Health (CDRH) reviewed the PMA and concluded that the PMA contained sufficient valid scientific evidence to provide reasonable assurance of the safety and effectiveness of the device for the prescribed indications for use. This PMA was not referred to Ophthalmic Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA submission duplicated information previously reviewed by the panel. CDRH approved this PMA in a letter to the applicant dated FEB 13 1997 , and signed by the Director, Office of Device Evaluation.

FEB 13 1997

Labeling

PLEASE READ THIS PACKAGE INSERT CAREFULLY AND KEEP FOR FUTURE USE.

2-IN-1 DROP
FOR USE WITH SOFT (HYDROPHILIC) AND RIGID GAS PERMEABLE CONTACT LENSES
(including lenses prescribed for frequent replacement)

DESCRIPTION: The 2-In-1 Drop is a sterile, PRESERVATIVE FREE, borate buffered, isotonic solution containing bendazac lysine 0.25%, hydroxypropyl methylcellulose 0.25% and potassium chloride in purified water.

ACTIONS: The 2-In-1 Drop, packaged in the single-use container, rewets and helps to remove particulate material from the surface of contact lenses during lens wear and assists in maintaining normal lens hydration.
The 2-In-1 Drop cushions lenses as a wetting solution during lens application.
The 2-In-1 Drop may also be used as a substitute for the daily cleaner in an appropriate chemical (not heat) disinfection regimen.

INDICATIONS: The 2-In-1 Drop, packaged in the single-use container, is indicated for use with soft (hydrophilic) contact lenses (including disposables) and rigid gas permeable contact lenses as a lubricating and rewetting agent during the wearing period and as a wetting agent to cushion lenses prior to placement on the eye. The 2-In-1 Drop may also be used in place of a daily cleaner as part of an appropriate chemical disinfection regimen.

CONTRAINDICATIONS (Reasons not to Use): **DO NOT** use the 2-In-1 Drop if you are allergic to any ingredient in it.

WARNINGS:

DO NOT confuse use of this product with other contact lens cleaners which cannot be used in the eye as a lubricating/rewetting drop. Other contact lens cleaners could cause severe eye irritation, including burning and stinging, if placed directly in the eye.

TO AVOID CONTAMINATION:

- DISCARD UNIT-DOSE CONTAINER IMMEDIATELY AFTER EACH USE. DO NOT SAVE UNUSED CONTENTS.
- DO NOT touch tip of container to any surface.
- DO NOT touch tip of container directly to the eye. Eye injury may result.

8341

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. It is essential that you follow your eye care practitioner's directions and all labeling instructions for proper use and care of your lenses and care products, including the lens case. EYE PROBLEMS, INCLUDING CORNEAL ULCERS, CAN DEVELOP RAPIDLY AND LEAD TO LOSS OF VISION; THEREFORE, IF YOU EXPERIENCE EYE DISCOMFORT, EXCESSIVE TEARING, VISION CHANGES, OR REDNESS OF THE EYE, IMMEDIATELY REMOVE YOUR LENSES AND PROMPTLY CONTACT YOUR EYE CARE PRACTITIONER.

Contact lens wearers should schedule follow-up visits with their eye care practitioner as recommended.
Do not wear daily wear lenses overnight. Clinical studies have shown that the risk of serious adverse reactions is increased when these lenses are worn overnight.

Remove extended wear lenses regularly for cleaning and disinfection, or for disposal and replacement, on the schedule prescribed by your eye care practitioner. Clinical studies have shown that there is an increased incidence of serious adverse reactions in extended wear contact lens use as compared to daily wear contact lens use. Studies have also shown that the risk of serious adverse reactions increases the longer extended wear lenses are worn before removal for cleaning and disinfection or for disposal and replacement.

Studies have also shown that smokers have a higher incidence of adverse reactions.

PRECAUTIONS:

TO AVOID CONTAMINATION:

Always wash and rinse your hands before handling your lenses.

DO NOT store opened container. Use immediately after opening.

DO NOT save unused contents.

Store solution at room temperature.

Use before the expiration date marked on the container tab and box.

Keep out of reach of children.

TO AVOID INJURY:

DO NOT touch dropper tip to your eye.

8332

ADVERSE REACTIONS (Problems and What to Do):

The following problems may occur with contact lens wear:

Eyes stinging, burning or itching (irritation)

Excessive watering (tearing) of the eye

Unusual eye secretions

Redness of the eye

Reduced sharpness of vision

Blurred vision

Sensitivity to light (photophobia)

Dry eyes

If you notice any of the above problems, **IMMEDIATELY REMOVE AND EXAMINE YOUR LENS.** If the discomfort or problem stops, then look closely at the lens.

If the lens is in any way damaged, **DO NOT** put the lens back on your eye. Place the lens in its storage case and call your eye care practitioner.

If the lens appears to be undamaged, disposable lens wearers should replace the lens with a fresh lens. Other wearers should thoroughly clean, rinse and disinfect the lens, then reinsert it. If the problem continues, **IMMEDIATELY** remove the lens and consult your eye care practitioner.

A serious condition such as infection, corneal ulcer, corneal vascularization or iritis may be present. Seek immediate professional identification of the problem, and, if necessary, obtain treatment to avoid serious eye damage.

For more information, refer to the Instructions for Wearers booklet for your specific contact lenses.

GENERAL LENS CARE DIRECTIONS:

Always wash, rinse and dry your hands before you handle your lenses.

Clean, rinse, and disinfect your lenses each time you remove them.
Note for disposable lens wearers: Discard and replace lenses each time they are removed.

8333 30

Always handle the same lens first to avoid mix-ups.

To prevent contamination and to avoid serious eye injury, always empty and rinse the lens case with a fresh recommended rinsing solution and allow case to air dry.

DIRECTIONS FOR USE:

Rewetting and Lubricating:

Use the 2-In-1 Drop up to 2-3 times a day, as needed or as directed by your eye care practitioner, while lenses are being worn, to moisten and lubricate your lenses and to relieve minor irritation, discomfort, and burning.

Twist the tab off the single-use container.

With your lenses on the eye, apply 2 or 3 drops of the 2-In-1 Drop in each eye and blink several times.

Discard container after each use. **DO NOT** save unused contents.

Caution: Excessive in-the-eye use of the 2-In-1 Drop to maintain comfortable lens wear may signify a condition that should be evaluated by your eye care practitioner.

Lens Wetting and Insertion:

Use the 2-In-1 Drop to cushion lens application.

Twist the tab off the single-use container.

Apply 2 or 3 drops of the 2-In-1 Drop over all surfaces of the lens without rubbing the lens.

Apply the lens to your eye as instructed by your eye care practitioner.

Repeat the procedure with the other lens.

Discard container after the wetting and insertion procedure is completed for both lenses.

Cleaning Prior to Disinfection:

You may also use the 2-In-1 Drop as a substitute for the daily cleaner in an appropriate chemical disinfection regimen.

Twist the tab off the single-use container.

After removing your lens, thoroughly clean by applying 1 or 2 drops of the 2-In-1 Drop to each lens surface and gently rubbing the lens for 10-15 seconds between the fingers or as directed by your eye care practitioner.

Thoroughly rinse the lens by rubbing the lens in a stream of a recommended rinsing solution. Soft (hydrophilic) contact lenses should never be rinsed with water.

Place the lens in the appropriate chamber of the lens storage case.

Repeat this procedure for the other lens.

Discard container after cleaning both lenses. **DO NOT** save unused contents.

If your lenses become visibly deposited or uncomfortable, you may require an alternate daily cleaner. Please consult with your eye care practitioner.

Disinfecting and Storing:

You must disinfect your lenses in a recommended chemical disinfecting solution. Do not soak lenses in the 2-In-1 Drop because it is not a disinfecting solution.

Disinfect and store your lenses according to the labeling instructions on your disinfecting and storage solution.

After the disinfection is completed and you have re-inserted your lenses, empty the lens storage case. Clean and rinse the storage case thoroughly; then allow it to air dry.

Clinical studies have demonstrated that some patients may not need to use an enzyme cleaner when they use the 2-In-1 Drop as directed.

HOW SUPPLIED: The 2-In-1 Drop is supplied in sterile, [PRESERVATIVE FREE,]
0.01 fl. oz. (0.3 ml) disposable single-use plastic containers that are packaged in boxes of 50 units each. Each container and the box are marked with the lot number and expiration date.

Manufactured for: Angelini Pharmaceuticals, Inc.
River Edge, NJ 07661, USA
Toll Free Telephone

No._____
Printed: Month/Year

33

OUTER BOX LABELING

Front Panel: 2-In-1 Drop
Bendazac Lysine 0.25% and Hydroxypropyl Methylcellulose
0.25%

Lubricating, Cushioning/Wetting, Rewetting

Daily Cleaner Substitute (for soft hydrophilic
and rigid gas permeable contact lenses)

Sterile and PRESERVATIVE FREE

Top Panel: 2-In-1 Drop
Bendazac Lysine 0.25% and Hydroxypropyl Methylcellulose
0.25%

Sterile and PRESERVATIVE FREE

Bottom Panel: 2-In-1 Drop
Bendazac Lysine 0.25% and Hydroxypropyl Methylcellulose 0.25%

Sterile and PRESERVATIVE FREE

Side Panel: Lot Number
Expiration Date

Back Panel:

Contents: Ten (10) Foil Pouches each containing 5 sterile PRESERVATIVE FREE 0.01 fl. oz. (0.3 ml) disposable single-use plastic containers. Each single-use plastic container contains Bendazac Lysine (0.25%), Boric Acid, Sodium Borate, Hydroxypropyl-methylcellulose (0.25%), Potassium Chloride in Purified Water.

Indications for Use:

The 2-In-1 Drop, packaged in the single-use container, is indicated for use with soft (hydrophilic) contact lenses (including disposables) and rigid gas permeable contact lenses as a wetting and rewetting agent during the wearing period and as a wetting agent to cushion lenses prior to placement on the eye. The 2-In-1 Drop may also be used as part of an appropriate

chemical disinfection regimen during the cleaning step.

Contraindications:

DO NOT use the 2-In-1 Drop if you are allergic to any ingredient in it.

See enclosed package insert for complete directions and important safety information.

Clinical studies have demonstrated that some patients may not need to use an enzyme cleaner when they use the 2-In-1 Drop as directed.

How Supplied:

The 2-In-1 Drop is supplied in sterile [PRESERVATIVE FREE,] 0.01 fl. oz. (0.3 ml) disposable single-use plastic containers that are packaged in boxes of 50 units each. Each container and the box are marked with the lot number and expiration date.

TAMPER RESISTANT STATEMENT: USE ONLY IF TAB AND SINGLE-USE CONTAINER ARE INTACT.

Manufactured for: Angelini Pharmaceuticals, Inc.

70 Grand Avenue
River Edge, NJ

07661

Toll Free

Telephone No._____

8338

FOIL POUCH LABELING

2-In-1 Drop
Bendazac Lysine 0.25% and Hydroxypropyl Methylcellulose 0.25%

Lubricating, Cushioning/Wetting, Rewetting

Daily Cleaner Substitute (for soft hydrophilic
and rigid gas permeable contact lenses)

TAMPER RESISTANT STATEMENT: USE ONLY IF TAB AND SINGLE-USE CONTAINER ARE INTACT.

[Lot Number and Expiration Date]

8339